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Post Marketing Surveillance of Anti-malarial Medicines in Tanzania

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Abstract

Background: Presence of substandard and falsified anti-malarial medicines is a major concern in countries with high prevalence of malaria. Systematic assessment and monitoring of anti-malarial medicines circulating on the market is critical to National Medicines Regulatory Authorities (NMRAs) in ensuring quality of these products in the fight against the burden of malaria disease.

Objectives: This survey was conducted by Tanzania Food and Drugs Authority (TFDA) with the aim of monitoring the quality of registered anti-malarial medicines circulating on the market in Tanzania Mainland.

Methodology: Purposive sampling method was used in obtaining the samples of anti-malarial medicines from 21 out of 26 regions of Tanzania Mainland between 2012 and 2015. These medicines were collected from ports of entry, domestic manufacturers, Medical Stores Department (MSD), wholesalers, hospitals, health centres, dispensaries and retail pharmacy outlets. Samples were subjected to product information review and quality screening using Global Pharma Health Fund® (GPHF) Mini-Lab kits. Samples failing or yielding doubtful results and ten percent (10%) of passed samples were subjected to tier two confirmatory testing using full pharmacopeial monographs at TFDA-WHO prequalified quality control laboratory.

Results: A total of 1,444 samples of oral solid formulations from different types of anti-malarials were sampled. Out of these, 132 (9.1%) failed labelling product information requirements. A high percentage of samples passed identification test by TLC (97.9%) and disintegration test (99.8%). A 4.8% (7/145) failure rate was observed in confirmatory testing of which one of the failed samples namely quinine sulphate 300 mg tablets was confirmed to be falsified.

Conclusion: These results indicate the importance of post marketing surveillance as an additional measure of assuring the quality of medicines by Regulators following marketing authorization and as a way of detecting falsified medicines circulating on the market.

Keywords: Post marketing surveillance; Medicines quality; TLC screening; Substandard; Falsified

Introduction

Malaria has killed many human beings more than any other disease and is still claiming millions of lives worldwide [1]. Nevertheless, the number of malaria cases and deaths reported have begun to fall down over years globally from an estimated 262 million in 2000 to 214 million in 2015, a decline of 18% [2]. In Africa, Asia and Latin America, malaria continues to be one of the diseases of public health importance [3] and in Tanzania malaria is a leading cause of morbidity and mortality especially for pregnant women and children under age five [4]. Malaria is an infective disease caused by sporozoan parasites and transmitted through a bite of infected Anopheles mosquito [5,6].

The battle against such life threatening disease need a number of combined efforts including preventive and management of malaria cases with good quality, safe and efficacious medicines [7]. However, this could be a nightmare especially in developing countries due to the fact that, availability and accessibility of appropriate medicines is a great concern [8,9]. It is estimated that about 270 million Africans have no access to medicines because they are either too expensive or unavailable, those with access to medicines face another setback of getting substandard or falsified ones that are in circulation due to inadequate control measures [9].

Presence of substandard and/or falsified anti-malarial medicines is a major concern in countries with high prevalence of malaria as it may lead to inadequate treatment and ultimately to development of drug resistance, which pose an urgent threat to vulnerable populations [10,11]. They also jeopardize progress and investment in combating malaria. A study has shown that, every year more than 122,000 African children under the age of five (5), lose their lives as a result of falsified and/or substandard anti-malarial medicines alone.

In recent years, various studies conducted in several African and Asian countries reported the widespread circulation of substandard and falsified medicines and anti-malarial medicines identified as the most frequently falsified at a rate of 92.7% [11-16]. A survey conducted

in Afghanistan in the year 2015 reported substandard quinine and Sulfadoxine/Pyrimethamine (SP) at rates of 32% (12/32) [17]. Another study conducted in Ghana and Togo reported presence of substandard and falsified ACT [15]. Likewise, poor quality ACT was observed on the market in Malawi [14].

Similar findings were reported in four studies conducted in Tanzania between 2000 and 2005, where 62.5% (5/8) of the tested SP using USP method failed dissolution test [18]. Another study by Minzi et al. [19] on the quality of amodiaquine and SP products marketed in Dar Es Salaam reported that, 13% of the amodiaquine samples failed dissolution test and 11% and 44% of SP samples failed assay and dissolution tests, respectively [19-22].

Hebron et al. investigated the chemical and pharmaceutical equivalence of 11 SP brands marketed in Tanzania whereby all samples complied with pharmacopoeial specifications for content. The samples were also tested for other quality indicating parameters and one brand failed hardness and disintegration tests, another brand failed hardness test while the third one failed friability test. Likewise, out of 304 anti-malarial products tested for quality, 12.2% which included antifolate anti-malarials, quinine tablets, amodiaquine formulations and 23.8% SP were found to be substandard [23].

A recent study conducted in six (6) sub-Saharan African countries revealed a failure rate of 11% of SP formulations among samples of anti-malarial medicines collected on the Tanzanian market. However, in this study all ACTs were found to comply with quality standards based on the fact that they were all sourced from single reputable supplier [12]. No other study was conducted in the era of multiple suppliers of ACTs and continuous use of SPs which were demonstrated to have poor quality.

The situation of substandard and/or falsified medicines on the market especially in malaria endemic countries is alarming and therefore systematic and continuous quality monitoring of anti-malarial medicines circulating on the market is critical to the national medicines regulatory authorities in ensuring quality of these products in the fight against the burden of malaria disease.

This survey was therefore conducted in order to assess the quality of anti-malarial medicines circulating on the Tanzanian market through Post Marketing Surveillance (PMS) programme. The objective was to ensure that the medicines maintain quality standards throughout their shelf life and also to enable the Authority to institute immediate measures for products that fail to meet quality standards in order to protect public health.

Methodology

Sampling

Purposive sampling method was used in obtaining the samples included in the survey. Samples were collected from 21 regions out of 26 in Tanzania Mainland namely; Iringa, Morogoro, Dodoma, Mtwara, Ruvuma, Shinyanga, Kagera, Singida, Rukwa, Geita, Kilimanjaro, Tanga, Coastal, Njombe, Mara, Dar Es Salaam, Mwanza, Arusha, Mbeya, Manyara and Kigoma. These regions were chosen based on the pre-defined criteria including regions bordering other countries and those with high prevalence of malaria. Sampling sites in these regions were selected in such a way as to cover ports of entry, domestic manufacturers and medicines from all formal levels (levels 1 and 2) of medicines distribution system in public and private sector. Level 1 is regarded as the highest level of distribution chain which included importers/wholesalers, the National Procurement Agency (NPA), the Medical Stores Department (MSD) and Level 2 consisted of various dispensing outlets including retail pharmacies, ADDOs, hospitals, health centres and dispensaries.

Trained TFDA and Local Government Drug Inspectors visited private sector drug outlets to purchase the anti-malarial medicines with associated information in their original packaging. While in the public drug outlets including MSD, samples were taken free of charge. TFDA informed the public sector in advance about the surveillance and requested them to allow inspectors to collect samples. Before leaving the premises, inspectors recorded information of the collected samples (i.e., name of drug, batch number, manufacturing and expiry dates, dates of collection and place, storage conditions and unit pack sizes) in the sample collection form and each sample collected was coded and packed in its own marked sampling bag and sealed. Collected samples were stored according to the manufacturers recommended storage conditions at TFDA zone offices before being transported to TFDA headquarters for quality evaluation.

Quality evaluation

Product information review: Correctness and legibility of information on the label of primary and secondary packaging of the samples and associated package inserts/patient leaflets were evaluated for each sample of anti-malarial medicine collected against TFDA approved labeling and insert requirements. The information checked were product name, dosage form and strength of medicine, name and address of the manufacturer, batch or lot number, registration number as well as manufacturing and expiry dates. Observations were recorded in PIR results forms.

Minilab drug screening: All samples that underwent product information review were then subjected to preliminary quality screening using Global Pharma Health Fund (GPHF) Mini-Lab kit methods where physicochemical testing [i.e., visual inspection and simple disintegration and Thin Layer Chromatography (TLC)] were performed.

Visual inspection: The appearance of the dosage forms were examined for discoloration, breaking, leaking or excessive powder/tablets/capsules.

Simple disintegration test: Simple disintegration testing was used to test the possibility of solid dosage forms (e.g. tablets) to break into small particles to indicate that the product can dissolve and undergo dissolution to release the active ingredient. This was done using a 100 ml wide neck glass bottle filled with water heated to 37°C. The tablets were shaken occasionally for about 30 min, and tablets that required more than 30 min to disintegrate were considered to have failed the test.

Thin layer chromatography: TLC method was used for qualitative determination of active ingredients, related substances and impurities present on the dosage forms. The method employed the principle of comparing properties of principal spots obtained by test and reference solutions in terms of color, shape, size, intensity and Retardation Factor (R_f) value.

Confirmatory testing: All samples that failed screening test and additional 10% of passed samples were taken for confirmatory testing by full monograph analysis in TFDA-WHO prequalified quality control laboratory. Parameters that were tested for the solid dosage

forms are appearance, identification, assay, related substances/ impurities (where applicable), dissolution and mass variation. For liquid dosage forms, appearance, identification, microbial limit, pH and assay were tested. Table 1 show outlines the analytical methods employed.

S. No.	Product name and dosage form	Method
1	Quinine tablets and syrup	In house (TFDA)
2	Quinine tablets	British Pharmacopoeia (BP 2011) for dissolution and related substances (other alkaloids)
3	Artemether/Lumefantrine tablets	In house (TFDA)
4	Sulfadoxine/Pyrimethamine tablets	International Pharmacopeia 4th edition
5	Sulfamethoxypyrazine/Pyrimethamine tablets	United States Pharmacopoeia
6	Dihydroartemisinin/Piperaquine tablets	Manufacturers method

Table 1: Outcome of GPHF Minilab screening method.

Results

Samples collected

A total of 1,444 samples of anti-malarial medicines were collected at ports of entry, domestic manufacturers and from both levels of medicines distribution supply chain in public and private pharmaceutical outlets as shown in Table 2. These were oral solid formulations from different types of anti-malarial medicines including 253 samples of Quinine tablets, 156 samples of Quinine syrups, 808 samples of fixed dose combinations of Artemether/Lumefantrine (ALU) tablets, 104 samples of Sulfadoxine/Pyrimethamine (SP) tablets and 72 samples of Sulfametopyrazine/Pyrimethamine tablets (SMP) and 51 of Dihydroartemisinin/Piperaquine (DHAP) tablets. Samples were collected from both domestically manufactured and imported medicines and two brands of each identified type of anti-malarials available in the selected premises were collected.

Medicines	Years				Total
	2012	2013	2014	2015	
Artemether/Lumefantrine (ALU) Tablets	200	201	204	203	808
Quinine Tablets	94	43	68	48	253
Quinine Syrup	64	28	26	38	156
Sulfadoxine/Pyrimethamine Tablets	15	38	24	27	104
Sulfamethoxypyrazine/Pyrimethamine Tablets	11	20	15	26	72
Dihydroartemisinin/Piperaquine Tablets	0	26	11	14	51
Total	517	429	425	398	1444

Table 2: Anti-malarial medicine samples.

Majority of the samples were collected from combination of ports of entry and domestic manufacturers (1150 samples, 79.6%) followed by hospitals (90 samples, 6.2%) and the fewest were from dispensaries (20 samples, 1.4%). Table 3 depicts distribution of samples obtained from different collection points.

Distribution level						
POEs and Domestic manufacturers	MSD	Pharmacy	Hospital	Dispensaries	Health Centre	ADDO
1,150 (79.6%)	25 (1.7%)	69 (5%)	90 (6.2%)	20 (1.4%)	34 (2.3%)	56 (3.9%)

Table 3: Samples of anti-malarials collected.

Product information review (PIR)

All samples collected were subjected to product information review of which a total of 132 (9.1%) samples failed to comply with product information requirements. The deficiencies identified include inappropriate/lack of storage conditions, lack of the name and address of manufacturers, discrepancy in address of manufacturers on the primary and secondary packaging and lack of package inserts or patient information leaflets. However, labels of packaging materials for all medicines appeared appropriate with stated name of product, strengths, dosage forms, batch numbers, and manufacturing and expiry dates. All anti-malarials collected were found to be registered in Tanzania albeit registration numbers were not indicated on labels of majority of samples.

Minilab drug screening

Visual inspection: A total of 4 samples (0.3%) failed visual inspection test out of 1,444 samples in which, discoloration was observed in two samples of quinine tablets.

Product name	Samples Tested	Disintegration		TLC		Visual inspection	
		Passed	Failed	Passed	Failed	Passed	Failed
ALU	808	808 (56%)	0	807 (55.8%)	1 (0.28%)	808 (56%)	0
Quinine tablets	253	253 (17.5%)	0	247 (17.1%)	6 (0.84%)	251 (17.4%)	2
Quinine syrup	156	156 (10.8%)	0	132 (9.1%)	24 (6.70%)	156 (10.8%)	0
Sulfadoxine/pyrimethamine tablets	104	103 (7%)	1	104 (7.2%)	0	103 (7.0%)	1
Sulfamethoxypyrazine/pyrimethamine tablets	72	71 (5%)	1	72 (5%)	0	72 (5.0%)	1
Duocotexin tablets	51	51 (3.5%)	0	51 (3.5%)	0	51 (3.5%)	0
Total	1444	1,442 (99.8%)	2 (0.2%)	1,413 (97.9%)	31 (2.1%)	1,440 (99.7%)	4 (0.3%)

Table 4: Results of Minilab drug screening method.

One Sample of Sulfamethopyrazine/Pyrimethamine and Second sample of Sulfadoxine/Pyrimethamine was observed to have undergone chipping.

Disintegration and TLC testing: Out of 1,444 samples subjected to disintegration and TLC testing, 1,413 samples (97.9%) complied with identification test by TLC and 1441/1444 (99.8%) complied with disintegration test.

Highest failure rate in identification test was attributed to Quinine syrup (6.7%) and generally failure in disintegration test was observed in SP formulations. Table 4 summarizes results of screening tests by Minilab test protocol (Table 4).

Confirmatory testing

A total of 145 samples of anti-malarial medicines were taken to confirmatory testing representing 81% (145/180) of the eligible number of samples. The rest of the required samples were expired and hence they were not taken to the laboratory for confirmatory testing. Results obtained have shown that a total of 7/145 samples (4.8%) failed and 95.2% (138/145) passed confirmatory testing by full monograph. Notably, all failed samples were products from domestic manufacturers. Kaale et al. made a similar observation with paracetamol from domestic manufacturers failing disintegration test [22].

Discussion

The results of this survey revealed higher number of ALU fixed dose combination products being imported into Tanzania as well as those circulating on the market compared to other types of anti-malarial medicines. This was attributed by the fact that ALU is the first line medicine for treatment of uncomplicated falciparum malaria in Tanzania [20].

Product information review was conducted on all samples collected and results of the survey indicated a small but significant failure rate in product information requirements (9.1%) which signifies the potential for importation and circulation on the market of medicinal products with product information different from the information approved during marketing authorization. The results provide a baseline data for anti-malarial medicines that do not meet labeling requirements yet still circulating on the market. This was the first recorded result on failure to product information requirements as previous studies did not carry out such evaluation because of different labeling requirements across the countries [13].

Screening test has shown the overall failure rates of 0.2 and 2.1% in disintegration test and identification by TLC methods, respectively. The failure rates were slightly higher compared to results obtained in Tanzania in previous surveys done by WHO on anti-malarial medicines in six sub-Saharan African countries where no failure on disintegration and identity were observed in the respective study. The observation is also consistent with the results of the previous study [13] in which for those countries with failures in minilab screening, the failure rate was due to TLC identity test (3 samples in Cameroon, 7 samples in Ethiopia, 6 samples in Ghana and 36 samples in Nigeria).

Alarmingly, within the group of samples which failed TLC identification test, a total of 24 out of 31 were quinine syrups which failed to show spots compared to the standard. In some instances, spots of samples were obtained but did not match those of the reference with respect to R_f and intensity. This observation provides a clue on poor stability and quality of liquid based quinine preparations circulating on the Tanzanian market.

Results of confirmatory testing did not show correlation between the semi-quantitative TLC and HPLC confirmatory results except for only one quinine 300 mg tablets which failed TLC identity test. This was later confirmed to be a falsified medicine by HPLC method. Surprisingly, majority of quinine syrups which failed TLC identity tests passed confirmatory test by HPLC and likewise one sample of ALU which was reported to have doubtful TLC results, was later confirmed to comply with full monograph testing. These two scenarios signify relatively less reliability of TLC identity method and stresses on the need for confirmatory tests before making conclusion on quality of medicines.

Results of confirmatory testing by full monograph demonstrated that none of the samples of ALU failed confirmatory testing by full monograph. A study which aimed to assess the quality of products in circulation in ADDOs in Tanzania concluded on a similar observation [22]. Failure in appearance, uniformity of weight and chipping of tablets was observed in samples of quinine tablets, Sulfamethoxypyrazine/Pyrimethamine tablets and Sulfadoxine/Pyrimethamine notably all of which were from domestic manufacturers. Results were consistent with the results reported in previous WHO study on quality of anti-malarial medicines in six Sub-Saharan African countries [13]. Consistency in observed failure in quality parameters could be ascribed by inadequate controls in product development and manufacturing by domestic manufacturers [21].

Substandard Quinine and Sulfadoxine/Pyrimethamine type of anti-malarials were also reported in the survey conducted in Afghanistan [10]. Although this survey confirmed the quality of ALU found on the Tanzanian market, poor quality ACTs were found in Malawi in 2015 [7]. Similar findings were reported in Ghana and Togo in the year 2014 where low content of artemisinin component was observed in fixed dose ACTs [12].

Conclusion

Despite the continued efforts put in place by TFDA in ensuring that medicines circulating on the market are of good quality, safe and efficacious through pre-registration assessment, screening the quality of products at ports of entry and regular inspection and surveillance of products, poor quality medicines were still detected on the market. Although appropriate regulatory actions have been taken including recall of substandard batches and removal of falsified medicines on the market, this survey has revealed the need for continued and strategic implementation of post marketing surveillance programme as one of the important regulatory functions especially in developing countries.

In addition, the results provide information on potential formulation related quality defects especially liquid quinine preparations, which can have deleterious implications as a result of potential treatment failures in paediatric patients. Results obtained from this survey also call for deliberate efforts by various players in addressing the challenge of manufacturing good quality medicines by domestic manufacturers.

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